The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: ESS100732
Title: A Phase IIIB, Randomized, Open-Label, Multicenter Study of the Safety and Efficacy of GW433908 (700mg BID) plus ritonavir (100mg BID) Versus Lopinavir/ritonavir (400mg/100mg BID) when Administered in Combination with the Abacavir/Lamivudine (600mg/300mg) Fixed Dose Combination Tablet QD in Antiretroviral-Naïve HIV-1 Infected Adults Over 48 Weeks.
Rationale: Lopinavir-ritonavir (LPV/r) is a preferred protease inhibitor for initial HIV-1 treatment. Fosamprenavir (GW433908, FPV)-ritonavir (r) plus two nucleoside reverse transcriptase inhibitors has shown similar efficacy and safety to LPV/r, but has not been directly compared in antiretroviral-naïve patients.
Phase: IIIB
Study Period: 25 May 2004 to 05 Feb 2006
Study Design: A 2-arm, parallel group, open-label, randomized, multicenter study.
Centers: 131 sites in 13 countries; 62 in the US, 8 in Canada, and 61 in Europe
Indication: HIV
Treatment: After a screening period (of up to 28 days), all eligible subjects were randomized 1:1 to receive: FPV 700mg BID + ritonavir 100mg BID + ABC 600mg/3TC 300mg FDC QD **OR** Lopinavir 400mg/ritonavir 100mg BID + ABC 600mg/3TC 300mg FDC QD
Objectives: To compare the efficacy, safety, and tolerability of FPV/r BID versus LPV/r BID when administered in combination with abacavir (ABC)/lamivudine (3TC) fixed dose combination (FDC) QD over 48 weeks in antiretroviral (ART)-naïve HIV-1 infected subjects.
Primary Outcome/Efficacy Variable: The primary endpoints were the proportion of subjects with HIV-1 RNA levels <400 copies/mL at 48 weeks and the proportion of subjects who permanently discontinued randomized treatment due to AEs.
Secondary Outcome/Efficacy Variable(s): Secondary endpoints included the proportion of subjects with HIV-1 RNA levels <400 copies/mL at Week 24; proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 and 48; absolute values and change from baseline plasma HIV-1 RNA and CD4+ cell counts, time to virologic failure, time to loss of virologic response (TLOVR), incidence of AEs, change from baseline in fasting lipid parameters, adherence based on pill counts, steady-state plasma APV trough concentrations, and development of genotypic and phenotypic resistance at virologic failure.
Statistical Methods: A targeted sample size of 433 subjects in each treatment group was determined based on having at least 90% power to declare non-inferiority of the FPV/r arm to the LPV/r arm within a 12% margin at the one-sided 0.025 significance level. The primary efficacy analysis was performed using the proportion of subjects with plasma HIV-1 RNA <400 copies/mL as determined by the TLOVR algorithm. The response proportions were compared by constructing a 95% confidence interval on the treatment difference (FPV/r minus LPV/r). Non-inferiority of the FPV/r arm to the LPV/r would be demonstrated if the lower bound of the 95% confidence interval was greater than -0.12. The confidence interval was calculated based on the normal approximation and stratified by the baseline plasma HIV-1 RNA category (<100,000 copies/mL or ≥100,000 copies/mL) using Mantel Haenszel weights. The proportion of subjects with plasma HIV-1 RNA <400 copies/mL and the proportion of subjects with plasma HIV-1 RNA <50 copies/mL were tabulated by study week and treatment group. Summary statistics were also provided for the observed absolute and change from baseline in plasma HIV-1 RNA levels and CD4+ cell counts by study week and treatment group. Treatment emergent AEs, clinical laboratory evaluations, and fasting lipid parameters were summarized. The primary efficacy population was the intent-to-treat exposed (ITT(E)) population which consisted of all randomized subjects who were treated before withdrawal from study. The safety population consisted of all subjects exposed to investigational product. The pharmacokinetic (PK) parameter population consisted of subjects for whom plasma amprenavir (APV) trough concentrations ($C\tau$) were available.

Study Population: Male and non-pregnant female subjects using adequate contraception were eligible for the study if they were ≥18 years of age and infected with HIV. Subjects were antiretroviral therapy naïve (defined as having ≤14 days of prior therapy with a nucleoside reverse transcriptase inhibitor [NRTI] and no prior therapy with a protease inhibitor [PI] or non-nucleoside reverse transcriptase inhibitor [NNRTI]) and had plasma HIV-1 RNA concentration ≥1000 copies/mL at screening.

Number of Subjects:

	FPV/r	LPV/r
Planned, N	433	433
Randomized, N	443	444
ITT(E)	434	444
Completed, n (%), ITT(E)	334 (77)	345 (78)
Total Number Subjects Withdrawn, n (%), ITT(E)	100 (23)	99 (22)
Withdrawn due to Adverse Events, n (%), ITT(E)	27 (6)	25 (6)
Withdrawn due to Lack of Efficacy[a], n (%), ITT(E)	9 (2)	9 (2)
Withdrawn for Other Reasons, n (%), ITT(E)	64 (15)	65 (15)

a. Includes protocol defined virologic failure and insufficient viral load response

Demographics:

	FPV/r	LPV/r
N (ITT(E))	434	444
Females: Males	96:338	96:348
Mean Age, years (standard deviation [SD])	39 (10.3)	38 (10.2)
White/Caucasian, n (%)	264 (61)	247 (56)

Primary Efficacy Results:

Proportion of subjects with plasma HIV-1 RNA < 400 copies/mL*; ITT(E) Population, TLOVR analysis

	FPV/r (N=434) %	LPV/r (N=444) %
Week 48	72.5%	71.4%
Stratified treatment difference (95% confidence interval)	1.1% (-4.84%, 7.05%)	

* Adjusted for the baseline HIV-1 RNA strata (HIV-1 RNA <100,000 copies/mL or ≥100,000 copies/mL).

Proportion of Subjects Permanently Discontinuing Randomized Treatment due to an Adverse Event (AE); Safety Population

	FPV/r (N=436) n (%)	LPV/r (N=443) n (%)
Subjects discontinuing randomized treatment due to an AE	53 (12)	43 (10)

Secondary Efficacy Results:		
Proportion of Subjects with Plasma HIV-1 RNA < 400 copies/mL; ITT(E) Population, TLOVR analysis		
	FPV/r (N=434) n (%)	**LPV/r (N=444) n (%)**
Week 24	358 (82)	376 (85)
Proportion of Subjects with Plasma HIV-1 RNA < 50 copies/mL; ITT(E) Population, TLOVR analysis		
Week 24	293 (68)	320 (72)
Week 48	285 (66)	288 (65)

Median Plasma HIV-1 RNA and Median Change from Baseline (log_{10} copies/mL); Observed analysis								
	Plasma HIV-1 RNA				**Change from Baseline**			
	FPV/r N=434		**LPV/r N=444**		**FPV/r N=434**		**LPV/r N=444**	
	n	**Median**	**n**	**Median**	**n**	**Median Change**	**n**	**Median Change**
Baseline	434	5.08	444	5.06	-		-	
Week 24	375	1.69	389	1.69	375	-3.32	389	-3.27
Week 48	328	1.69	341	1.69	328	-3.34	341	-3.33

Median CD4+Cell Count and Median Change from Baseline (cells/mm^3); Observed analysis								
	CD4+ Cell Count				**Change from Baseline**			
	FPV/r N=434		**LPV/r N=444**		**FPV/r N=434**		**LPV/r N=444**	
	n	**Median**	**n**	**Median**	**n**	**Median Change**	**n**	**Median Change**
Baseline	434	188	444	194	-		-	
Week 24	371	325	388	343	371	128	388	141
Week 48	323	375	336	397	323	176	336	191

Adherence by Pill Count* over 48 Weeks; ITT(E) Population		
	FPV/r N=434	**LPV/r N=444**
FPV/r or LPV/r		
n	233	239
Median % adherence	98.4%	98.0%
ABC/3TC FDC		
n	254	266
Median % adherence	99.4%	99.4%

* % adherence = (no. of pills dispensed – no. of pills returned)(no. of pills prescribed)

Pharmacokinetics (Subjects in the PK Parameter Population)		
	FPV/r N=363	**LPV/r**
Plasma APV Cτ (μg/mL), geometric mean (95% CI)	2.62 (2.46-2.80)	N/A

Resistance through 48 Weeks; ITT(E) Population		
	FPV/r N=434	**LPV/r N=444**
Subjects with confirmed virologic failure	**16**	**24**
Unable to sequence	2	3
No treatment-emergent mutations	9	14
Treatment-emergent mutations (n)*		
TAM-associated mutations (M41M/L)	0	1
3TC-associated mutations (M184I, M184V, M184M/V)	3	4
NNRTI-associated mutations (V106V/A)	0	2
PI-associated mutations – all minor (I54I/L, I93I/L, K20K/R, I62I/V)	3	2

*No treatment-emergent reduced phenotypic susceptibility to FPV/r or LPV/r per IAS-USA resistance guidelines, Oct. 2005

Time to Virologic Failure, ITT(E) Population
There were too few subjects meeting the definition of virologic failure to calculate the median time to virologic failure in the ITT(E) population using the Kaplan-Meier method.

Summary of Fasting Lipids; Safety Population				
	FPV/r (n=436)		**LPV/r (n=443)**	
	Median Change from Baseline at Week 48		**Median Change from Baseline at Week 48**	
mg/dL	**n**	**Median (IQR)**	**n**	**Median (IQR)**
Total cholesterol	250	62 (32-87)	261	56 (27-80)
LDL	212	31 (8-52)	226	20 (-2-43)
HDL	246	12 (6-19)	253	14 (7-21)
Triglycerides	250	62 (17-140)	261	73 (21-137)

Safety Results (Safety Population): An on therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication.

Most Frequent Adverse Events – On-Therapy (Safety Population)	**FPV/r (N=436) n (%)**	**LPV/r (N=443) n (%)**
Subjects with any AE(s)	**415 (95)**	**404 (91)**
Diarrhoea	224 (51)	210 (47)
Nausea	127 (29)	106 (24)
Headache	69 (16)	61 (14)
Fatigue	62 (14)	40 (9)
Nasopharyngitis	58 (13)	40 (9)
Vomiting	58 (13)	38 (9)
Upper respiratory tract infection	42 (10)	32 (7)
Rash	42 (10)	28 (6)
Pyrexia	37 (8)	38 (9)
Cough	36 (8)	37 (8)
Depression	29 (7)	31 (7)
Influenza	23 (5)	31 (7)

Serious Adverse Events - On-Therapy (Safety Population) n (%) [n considered by the investigator to be related to study medication] -Includes both fatal and non-fatal events		
	FPV/r (N=436) n (%) [related]	**LPV/r (N=443) n (%) [related]**
Subjects with any SAE (s)	**69 (16) [37]**	**57 (13) [26]**
Drug hypersensitivity[a]	32 (7) [32]	21 (5) [21]
Immune reconstitution syndrome	0	1 (<1) [0]
Pneumonia	4 (<1) [0]	2 (<1) [0]
Cellulitis	2 (<1) [0]	0 [0]
Mycobacterium avium complex infection	1 (<1) [0]	1 (<1) [0]
Syphilis	1 (<1) [0]	1 (<1) [0]
Urinary tract infection	2 (<1) [0]	0
Bronchititis	0	1 (<1) [0]
Campylobacter gastroenteritis	0	1 (<1) [0]
Campylobacter intestinal infection	0	1 (<1) [0]
Catheter sepsis	0	1 (<1) [0]
Clostridium difficile colitis	0	1 (<1) [0]
Cytomegalovirus duodenitis	1 (<1) [0]	0
Herpes oesophagitis	1 (<1) [0]	0
Herpes zoster	0	1 (<1) [0]
Influenza	0	1 (<1) [0]
Pancreatic abscess	0	1 (<1) [0]
Pyelonephritis	1 (<1) [0]	0
Secondary syphilis	0	1 (<1) [0]
Shigella infection	0	1 (<1) [0]
Sinusitits	1 (<1) [0]	0 [0]
Cerebrovascular accident	0	2 (<1) [0]
Dizziness	2 (<1) [1]	0
Tremor	2 (<1) [0]	0
Balance disorder	1 (<1) [1]	0
Cerebellar syndrome	1 (<1) [0]	0
Encephalitis	1 (<1) [0]	0
Headache	1 (<1) [1]	0
Hyporeflexia	1 (<1) [1]	0

Neuropathy	1 (<1) [1]	0
Neuropathy peripheral	0	1 (<1) [1]
Sciatica	1 (<1) [1]	0
Kaposi's sarcoma	2 (<1) [1]	0
Lymphoma	0	2 (<1) [0]
Burkitt's lymphoma	1 (<1) [0]	0
Hodgkin's disease	0	1 (<1) [0]
Papillary thyroid cancer	1 (<1) [0]	0
Small intestine carcinoma	0	1 (<1) [0]
Thyroid adenoma	1 (<1) [0]	0
Uterine leiomyoma	0	1 (<1) [0]
Diarrhoea	2 (<1) [1]	0
Pancreatitis	0	2 (<1) [1]
Abdominal pain	0	1 (<1) [1]
Gastrointestinal haemorrhage	0	1 (<1) [0]
Gastrooesophageal reflux disease	1 (<1) [1]	0
Pancreatitis acute	0	1 (<1) [1]
Depression	2 (<1) [0]	1 (<1) [0]
Suicide attempt	1 (<1) [0]	1 (<1) [0]
Alcoholism	1 (<1) [0]	0
Anxiety	1 (<1) [0]	0
Conversion disorder	1 (<1) [0]	0
Depressed mood	1 (<1) [0]	0
Insomnia	1 (<1) [0]	0
Mental status change	0	1 (<1) [0]
Psychotic disorder	0	1 (<1) [0]
Stress	1 (<1) [0]	0
Chest pain	2 (<1) [0]	1 (<1) [0]
Pyrexia	2 (<1) [0]	0
Drug interaction	0	1 (<1) [1]
Irritability	1 (<1) [0]	0
Non-cardiac chest pain	1 (<1) [0]	0
Myocardial infarction	2 (<1) [0]	1 (<1) [0]
Cardiac failure congestive	0	1 (<1) [0]
Coronary artery disease	1 (<1) [0]	0
Tachyarrhythmia	1 (<1) [1]	0
Diabetic ketoacidosis	0	2 (<1) [0]
Dehydration	1 (<1) [0]	0
Hypoglycemia	0	1 (<1) [0]
Asthma	1 (<1) [0]	1 (<1) [0]
Dyspnoea	1 (<1) [0]	0
Dyspnoea exacerbated	0	1 (<1) [0]
Interstitial lung disease	1 (<1) [0]	0
Anaemia	1 (<1) [0]	2 (<1) [0]
Neutropenia	1 (<1) [0]	0
Cholecystitis	0	1 (<1) [0]
Hepatic cirrhosis	0	1 (<1) [0]
Hepatotoxicity	1 (<1) [1]	0
Lower limb fracture	0	1 (<1) [0]
Multiple fractures	0	1 (<1) [0]
Skull fracture	1 (<1) [0]	0
Blood creatinine increased	0	1 (<1) [0]
Cardiac murmur	1 (<1) [0]	0
Transaminases increased	0	1 (<1) [1]
Vertigo	1 (<1) [0]	1 (<1) [1]

Nephrolithiasis	1 (<1) [0]	0
Renal failure acute	1 (<1) [0]	0
Stevens-Johnson syndrome	1 (<1) [0]	1 (<1) [0]
Foetal malformation	1 (<1) [1]	0
Goitre	0	1 (<1) [0]
Intervertebral disc protrusion	1 (<1) [0]	0
Abortion spontaneous	0	1 (<1) [0]
Hypotension	0	1 (<1) [0]

a. All cases of drug hypersensitivity were abacavir hypersensitivity. All hypersensitivity reactions to abacavir were reported as SAEs regardless of whether the event fulfilled the International Conference on Harmonization E2A definition of serious.

Fatal SAEs, n (%) [n considered by the investigator to be related to study medication]		
	FPV/r (N=436) n (%) [related]	**LPV/r (N=443) n (%) [related]**
Subjects with fatal SAE (s)	**4 (1) [0]**	**1 (<1) [0]**
Mycobacterium avium complex infection	1 (<1) [0]	0
Cytomegalovirus duodenitis	1 (<1) [0]	0
Herpes osophagitis	1 (<1) [0]	0
Cerebellar syndrome	1 (<1) [0]	0
Encephalitis	1 (<1) [0]	0
Kaposi's sarcoma	1 (<1) [0]	0
Lymphoma	0	1 (<1) [0]
Pyrexia	1 (<1) [0]	0
Skull fracture	1 (<1) [0]	0
Stevens-Johnson syndrome	1 (<1) [0]	0

Conclusion:
See publication below.

Publications:
Eron JJ, Yeni P, Gathe JC, et al. The KLEAN Study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir/lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet*, 2006. 368: 476-82.

Date Updated: 21-Sep-2006